

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of : Dasseux, *et al.*

Serial No.:to be assigned

Filed: Herewith

Group Art Unit: to be assigned

For: APOLIPOPROTEIN A-I
AGONIST AND THEIR USE TO
TREAT DYSLIPIDEMIC DISORDERS

Attorney Docket No.: 9196-022-999

PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.115

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In accordance with Rule 115 of the Rules of Practice, please enter the following
amendments prior to examination of the above-captioned application.

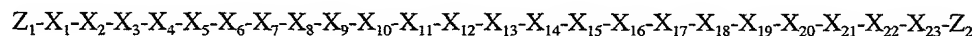
AMENDMENTS

IN THE CLAIMS

Please cancel Claims 2, 19, 28, 30-33, 36, 38-41, 43 and 45-53 without prejudice.

Please amend Claims 1, 3-18, 20-27, 29, 37, 42, 44 and 54 to read as follows:

1. (Amended) An ApoA-I agonist compound comprising:
 - (i) a 22 to 29-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

- X_1 is D-Ala (a), Gly (G), D-Gln (q), D-Asn (n), D-Asp (d) or D-Pro (p);
- X_2 is a D-enantiomeric aliphatic residue;
- X_3 is D-Leu (l) or D-Phe (f);
- X_4 is a D-enantiomeric acidic residue;
- X_5 is D-Leu (l) or D-Phe (f);
- X_6 is D-Leu (l) or D-Phe (f);
- X_7 is a D-enantiomeric hydrophilic residue;
- X_8 is a D-enantiomeric acidic or a basic residue;
- X_9 is D-Leu (l) or Gly (G);
- X_{10} is D-Leu (l), D-Trp (w) or Gly (G);
- X_{11} is a D-enantiomeric hydrophilic residue;
- X_{12} is a D-enantiomeric hydrophilic residue;
- X_{13} is Gly (G) or a D-enantiomeric aliphatic residue;
- X_{14} is D-Leu (l), D-Trp (w), Gly (G) or D-Nal;
- X_{15} is a D-enantiomeric hydrophilic residue;
- X_{16} is a D-enantiomeric hydrophobic residue;
- X_{17} is a D-enantiomeric hydrophobic residue;
- X_{18} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;
- X_{19} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;
- X_{20} is a D-enantiomeric basic residue;
- X_{21} is a D-enantiomeric aliphatic residue;
- X_{22} is a D-enantiomeric basic residue;
- X_{23} is absent or a D-enantiomeric basic residue;
- Z_1 is R_2N^- or $RC(O)NR^-$;

Z_2 is $-C(O)NRR$, $-C(O)OR$ or $-C(O)OH$ or a salt thereof;

each R is independently $-H$, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl, (C_5-C_{20}) aryl, (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic; and

each " - " between residues X_1 through X_{23} independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 28-residue deleted D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20} , X_{21} and X_{22} are optionally deleted; or

(iii) a 22 to 29-residue altered D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one of residues X_1 , X_2 , X_3 , X_4 , X_5 , X_6 , X_7 , X_8 , X_9 , X_{10} , X_{11} , X_{12} , X_{13} , X_{14} , X_{15} , X_{16} , X_{17} , X_{18} , X_{19} , X_{20} , X_{21} , X_{22} or X_{23} is conservatively substituted with another D-enantiomeric residue.

3. (Amended) The ApoA-I agonist compound of Claim 1 which is the altered D-enantiomeric peptide or peptide analogue according to formula (I).

4. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophobic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

5. (Amended) The ApoA-I agonist compound of Claim 4 in which:

X_1 is D-Pro (p), Gly (G) or D-Ala (a);

X_2 is D-Ala (a), D-Leu (l) or D-Val (v);

X_3 is D-Leu (l) or D-Phe (f);

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X₉ is D-Leu (l) or Gly (G);
X₁₀ is D-Leu (l), D-Trp (w) or Gly (G);
X₁₃ is D-Leu (l), Gly (G) or D-Aib;
X₁₄ is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);
X₁₆ is D-Ala (a), D-Nal, D-Trp (w), Gly (G), D-Leu (l) or D-Phe (f);
X₁₇ is D-Leu (l), Gly (G) or D-Nal;
X₂₁ is D-Leu (l); and

at least one of X₄, X₇, X₈, X₁₁, X₁₂, X₁₅, X₁₈, X₁₉, X₂₀, X₂₂ and X₂₃ is conservatively substituted with another D-enantiomeric residue.

6. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophilic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

7. (Amended) The ApoA-I agonist compound of Claim 6 in which:

X₄ is D-Asp (d) or D- Glu (e);
X₇ is D-Lys (k), D-Arg (r) or D-Orn;
X₈ is D-Asp (d) or D-Glu (e);
X₁₁ is D-Asn (n) or D-Gln (q);
X₁₂ is D-Glu (e) or D-Asp (d);
X₁₅ is D-Asp (d) or D-Glu (e);
X₁₈ is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
X₁₉ is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
X₂₀ is D-Lys (k) or D-Orn;
X₂₂ is D-Lys (k) or D-Orn;
X₂₃ is absent or D-Lys (k); and

at least one of X₁, X₂, X₃, X₅, X₆, X₉, X₁₀, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.

8. (Amended) The ApoA-I agonist compound of Claim 7 in which X₃ is D-Leu (l) or D-Phe (f), X₆ is D-Phe (f), X₉ is D-Leu (l) or Gly (G), X₁₀ is D-Leu (l) or D-Trp (w) or Gly

(G) and at least one of X₁, X₂, X₅, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.

9. (Amended) The ApoA-I agonist compound of Claim 4 or 6 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.

10. (Amended) The ApoA-I agonist compound of Claim 1 which is the deleted D-enantiomeric peptide or peptide analogue according to formula (I).

11. (Amended) The ApoA-I agonist compound of Claim 10 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.

12. (Amended) The ApoA-I agonist compound of Claim 1 which is a 22-23 residue D-enantiomeric peptide or peptide analogue according to formula (I).

13. (Amended) The ApoA-I agonist compound of Claim 12 in which:
the "-" between residues designates -C(O)NH-;
Z₁ is H₂N-; and
Z₂ is -C(O)OH or a salt thereof.

14. (Amended) The ApoA-I agonist compound of Claim 13, in which:
X₁ is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q), D-Asp (d) or D-Pro (p);
X₂ is D-Ala (a), D-Val (v) or D-Leu (l);
X₃ is D-Leu (l) or D-Phe (f);
X₄ is D-Asp (d) or D-Glu (e);
X₅ is D-Leu (l) or D-Phe (f);
X₆ is D-Leu (l) or D-Phe (f);
X₇ is D-Lys (k), D-Arg (r) or D-Orn;
X₈ is D-Asp (d) or D-Glu (e);
X₉ is D-Leu (l) or Gly (G);

X_{10} is D-Leu (l), D-Trp (w) or Gly (G);
 X_{11} is D-Asn (n) or D-Gln (q);
 X_{12} is D-Glu (e) or E-Asp (d);
 X_{13} is Gly (G), D-Leu (l) or D-Aib;
 X_{14} is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);
 X_{15} is D-Asp (d) or D-Glu (e);
 X_{16} is D-Ala (a), D-Nal, D-Trp (w), D-Leu (l), D-Phe (f) or Gly (G);
 X_{17} is Gly (G), D-Leu (l) or D-Nal;
 X_{18} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
 X_{19} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
 X_{20} is D-Lys (k) or D-Orn;
 X_{21} is D-Leu (l);
 X_{22} is D-Lys (k) or D-Orn; and
 X_{23} is absent or D-Lys (k).

15. (Amended) The ApoA-I agonist compound of Claim 14, in which X_{23} is absent.
16. (Amended) The ApoA-I agonist compound of Claim 13 or 14, in which one of X_{18} or X_{19} is D-Gln (q) or D-Asn (n) and the other of X_{18} or X_{19} is D-Lys (k) or D-Orn.
17. (Amended) The ApoA-I agonist compound of Claim 14 in which each of X_9 , X_{10} , X_{13} , X_{14} , X_{15} and X_{17} is other than Gly (G).
18. (Amended) The ApoA-I agonist compound of Claim 14 in which one of X_9 , X_{10} , X_{13} , X_{14} , X_{15} and X_{17} is Gly (G) and the others are other than Gly (G).
20. (Amended) A multimeric ApoA-I agonist compound which comprises formula (II):



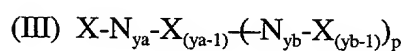
or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;
n is an integer from 0 to 10;
each "HH" is independently a peptide or peptide analogue according to

Claim 1;

each "LL" is independently a bifunctional linker; and
each " - " independently designates a covalent linkage.

21. (Amended) A multimeric ApoA-I agonist compound which comprises formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $\text{HH-(LL}_m\text{—HH)}_n\text{LL}_m\text{—HH}$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

N_{y_a} and N_{y_b} are each independently a multifunctional linking moiety where y_a

and y_b represent the number of functional groups on N_{y_a} and N_{y_b} , respectively;

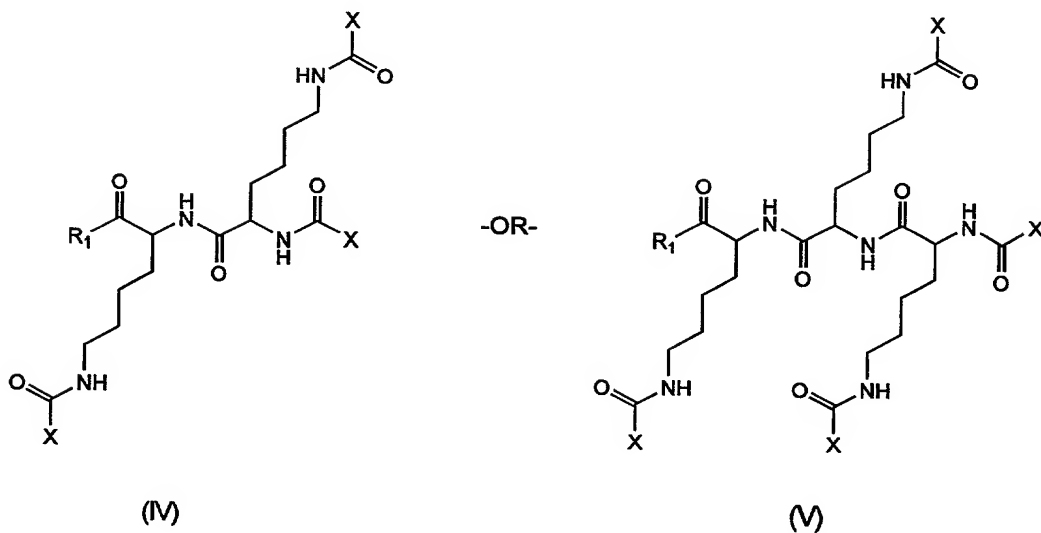
each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each "—" independently designates a covalent bond.

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or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $\text{HH}-(\text{LL}_m-\text{HH})_n\text{LL}_m-\text{HH}$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R₁ is -OR or -NRR; and

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl; (C₅-C₂₀) aryl (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

23. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which the bifunctional linker is cleavable.

24. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which n is 0.
25. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which m is 0.
26. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 21 in which each HH is independently a peptide or peptide analogue according to Claim 3.
27. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a peptide or peptide analogue according to Claim 10.
29. (Amended) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.
34. (Amended) The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.
35. (Amended) The ApoA-I agonist-lipid complex of Claim 34 which is in the form of a lyophilized powder.
37. (Amended) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

42. (Amended) The pharmaceutical composition of Claim 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

44. (Amended) A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

54. (Amended) A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

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REMARKS

With this Amendment, Applicants have canceled Claims 2, 19, 28, 30-33, 36, 38-41, 43 and 45-53 without prejudice. Claims 1, 3-18, 20-27, 29, 37, 42, 44 and 54 have been amended. After entry of the instant amendment, Claims 1, 3-18, 20-27, 29, 34-35, 37, 42, 44 and 54-56 are pending. For the Examiner's convenience, marked up copy of the claims is attached as Exhibit A. A copy of all pending claims upon entry of the instant amendment is attached as Exhibit B.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

I. THE AMENDMENT OF THE CLAIMS

In general, the claims have been amended to recite D-enantiomeric ApoA-I agonist compounds, lipid complexes, pharmaceutical compositions and methods of use thereof. Support for amended Claims 1, 3-18, 20-27, 29, 37, 42, 44 and 54 may be found, for example, in Claims 1, 3-18, 20-27, 29, 37, 42, 44 and 54 as originally filed and in the specification, for example, at page 44, lines 15 to 29.

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CONCLUSION

Applicants submit that Claims 1, 3-18, 20-27, 29, 34-35, 37, 42, 44 and 54-56 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

No fee is believed due in connection with this response. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-022-999). A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: March 15, 2002



Rahul Pathak (Reg No.) 42,983
for Laura A. Coruzzi 30,742
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

COPY

CONCLUSION

Applicants submit that Claims 1, 3-18, 20-27, 29, 34-35, 37, 42, 44 and 54-56 satisfy all the criteria for patentability and are in condition for allowance. An early indication of the same is therefore kindly solicited.

No fee is believed due in connection with this response. However, pursuant to 37 C.F.R. §1.136 (a)(3), the Commissioner is authorized to charge all required fees, fees under 37 C.F.R. §1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds LLP, U.S. Deposit Account No. 16-1150 (Order No. 9196-022-999). A copy of this sheet is enclosed for accounting purposes.

Respectfully submitted,

Date: March 15, 2002


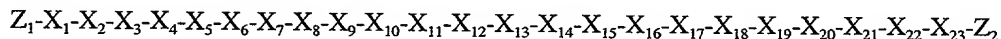
 42,983
Rahul Pathak (Reg No.)
for Laura A. Coruzzi 30,742
PENNIE & EDMONDS LLP
1155 Avenue of the Americas
New York, New York 10036-2711
(212) 790-9090

EXHIBIT A

Claim Amendment: Marked Up Copy

1. (Amended) An ApoA-I agonist compound comprising:
- (i) a [15] 22 to 29-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises [the structural] formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

X₁ is [Pro (P),] D-Ala [(A)] (a), Gly (G), D-Gln [(Q)] (q), D-Asn [(N)] (n), D-Asp [(D)] (d) or D-Pro (p);

X₂ is [an] a D-enantiomeric aliphatic residue;

X₃ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₄ is [an] D-enantiomeric acidic residue;

X₅ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₆ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₇ is a D-enantiomeric hydrophilic residue;

X₈ is [an] a D-enantiomeric acidic or a basic residue;

X₉ is D-Leu [(L)] (l) or Gly (G);

X₁₀ is D-Leu [(L)] (l), D-Trp [(W)] (w) or Gly (G);

X₁₁ is a D-enantiomeric hydrophilic residue;

X₁₂ is a D-enantiomeric hydrophilic residue;

X₁₃ is Gly (G) or [an] a D-enantiomeric aliphatic residue;

X₁₄ is D-Leu [(L)] (l), D-Trp [(W)] (w), Gly (G) or D-Nal;

X₁₅ is a D-enantiomeric hydrophilic residue;

X₁₆ is a D-enantiomeric hydrophobic residue;

X₁₇ is a D-enantiomeric hydrophobic residue;

X₁₈ is D-Gln [(Q)] (q), D-Asn [(N)] (n) or a D-enantiomeric basic residue;

X₁₉ is D-Gln [(Q)] (q), D-Asn [(N)] (n) or a D-enantiomeric basic residue;

X₂₀ is a D-enantiomeric basic residue;

X₂₁ is [an] a D-enantiomeric aliphatic residue;

X₂₂ is a D-enantiomeric basic residue;

X₂₃ is absent or a D-enantiomeric basic residue;

Z₁ is [H₂N- or RC(O)NH-] R₂N- or RC(O)NR-;

Z₂ is -C(O)NRR, -C(O)OR or -C(O)OH or a salt thereof;

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic; and

each " - " between residues [X_n] X₁ through X₂₃ independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 28-residue deleted [from of structural] D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, X₁₇, X₁₈, X₁₉, X₂₀, X₂₁ and X₂₂ are optionally deleted; or

(iii) [an] a 22 to 29-residue altered [form of structural] D-enantiomeric peptide or peptide analogue according to [of] formula (I) in which at least one of residues X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, X₁₇, X₁₈, X₁₉, X₂₀, X₂₁, X₂₂ or X₂₃ is conservatively substituted with another D-enantiomeric residue.

3. (Amended) The ApoA-I agonist compound of Claim 1 which is the altered [form of structural] D-enantiomeric peptide or peptide analogue according to formula (I).

4. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophobic residues are fixed according to [structural] formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

5. (Amended) The ApoA-I agonist compound of Claim 4 in which:

X₁ is [Pro (P)] D-Pro (p), Gly (G) or D-Ala [(A)] (a);

X₂ is D-Ala [(A)] (a), D-Leu [(L)] (l) or D-Val [(V)] (v);

X₃ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₅ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₆ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₉ is D-Leu [(L)] (l) or Gly (G);

X₁₀ is D-Leu [(L)] (l), D-Trp [(W)] (w) or Gly (G);

X₁₃ is D-Leu [(L)] (l), Gly (G) or D-Aib;

X₁₄ is D-Leu [(L)] (l), D-Nal, D-Trp [(W)] (w) or Gly (G);

X₁₆ is D-Ala [(A)] (a), D-Nal, D-Trp [(W)] (w), Gly (G), D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₁₇ is D-Leu [(L)] (l), Gly (G) or D-Nal;

X₂₁ is D-Leu [(L)] (l); and

at least one of X₄, X₇, X₈, X₁₁, X₁₂, X₁₅, X₁₈, X₁₉, X₂₀, X₂₂ and X₂₃ is conservatively substituted with another D-enantiomeric residue.

6. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophilic residues are fixed according to [structural] formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

7. (Amended) The ApoA-I agonist compound of Claim 6 in which:

X₄ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₇ is D-Lys [(K)] (k), D-Arg [(R)] (r) or D-Orn;

X₈ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₁₁ is D-Asn [(N)] (n) or D-Gln [(Q)] (q);

X₁₂ is D-Glu [(E)] (e) or D-Asp [(D)] (d);

X₁₅ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₁₈ is D-Gln [(Q)] (q), D-Asn [(N)] (n), D-Lys [(K)] (k) or D-Orn;

X₁₉ is D-Gln [(Q)] (q), D-Asn [(N)] (n), D-Lys [(K)] (k) or D-Orn;

X₂₀ is D-Lys [(K)] (k) or D-Orn;

X₂₂ is D-Lys [(K)] (k) or D-Orn;

X₂₃ is absent or D-Lys [(K)] (k); and

at least one of X₁, X₂, X₃, X₅, X₆, X₉, X₁₀, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.

8. (Amended) The ApoA-I agonist compound of Claim 7 in which X₃ is D-Leu [(L)] (l) or D-Phe [(F)] (f), X₆ is D-Phe [(F)] (f), X₉ is D-Leu [(L)] (l) or Gly (G), X₁₀ is D-Leu [(L)] (l) or D-Trp [(W)] (w) or Gly (G) and at least one of X₁, X₂, X₅, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.

9. (Amended) The ApoA-I agonist compound of Claim 4 or 6 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.

10. (Amended) The ApoA-I agonist compound of Claim 1 which is the deleted [form of structural] D-enantiomeric peptide or peptide analogue according to formula (I).

11. (Amended) The ApoA-I agonist compound of Claim 10 in which one or two helical [turn] turns of the peptide or peptide analogue is deleted.

12. (Amended) The ApoA-I agonist compound of Claim 1 which is a 22-23 residue D-enantiomeric peptide or peptide analogue [of structural] according to formula (I).

13. (Amended) The ApoA-I agonist compound of Claim 12 in which:

the "-" between residues designates -C(O)NH-;

Z₁ is H₂N-; and

Z₂ is -C(O)OH or a salt thereof.

14. (Amended) The ApoA-I agonist compound of Claim 13, in which:

X₁ is [Pro (P)] D-Ala [(A)] (a), Gly (G), D-Asn [(N)] (n), D-Gln [(Q)] (q),

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D-Asp [(D)] (d) or D-Pro (p);

X₂ is D-Ala [(A)] (a), D-Val [(V)] (v) or D-Leu [(L)] (l);

X₃ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₄ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₅ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₆ is D-Leu [(L)] (l) or D-Phe [(F)] (f);

X₇ is D-Lys [(K)] (k), D-Arg [(R)] (r) or D-Orn;

X₈ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₉ is D-Leu [(L)] (l) or Gly (G);

X₁₀ is D-Leu [(L)] (l), D-Trp [(W)] (w) or Gly (G);

X₁₁ is D-Asn [(N)] (n) or D-Gln [(Q)] (q);

X₁₂ is D-Glu [(E)] (e) or D-Asp [(D)] (d);

X₁₃ is Gly (G), D-Leu [(L)] (l) or D-Aib;

X₁₄ is D-Leu [(L)] (l), D-Nal, D-Trp [(W)] (w) or Gly (G);

X₁₅ is D-Asp [(D)] (d) or D-Glu [(E)] (e);

X₁₆ is D-Ala [(A)] (a), D-Nal, D-Trp [(W)] (w), D-Leu [(L)] (l), D-Phe [(F)]

(f) or Gly (G);

X₁₇ is Gly (G), D-Leu [(L)] (l) or D-Nal;

X₁₈ is D-Gln [(Q)] (q), D-Asn [(N)] (n), D-Lys [(K)] (k) or D-Orn;

X₁₉ is D-Gln [(Q)] (q), D-Asn [(N)] (n), D-Lys [(K)] (k) or D-Orn;

X₂₀ is D-Lys [(K)] (k) or D-Orn;

X₂₁ is D-Leu [(L)] (l);

X₂₂ is D-Lys [(K)] (k) or D-Orn; and

X₂₃ is absent or D-Lys [(K)] (k).

15. (Amended) The ApoA-I agonist compound of Claim 14, in which X₂₃ is absent.

16. (Amended) The ApoA-I agonist compound of Claim 13 or 14, in which one of X₁₈ or X₁₉ is D-Gln [(Q)] (q) or D-Asn [(N)] (n) and the other of X₁₈ or X₁₉ is D-Lys [(K)] (k) or D-Orn.

17. (Amended) The ApoA-I agonist compound of Claim 14 in which each of X₉, X₁₀, X₁₃, X₁₄, X₁₅ and X₁₇ is other than Gly (G).

18. (Amended) The ApoA-I agonist compound of Claim 14 in which one of X₉, X₁₀, X₁₃, X₁₄, X₁₅ and X₁₇ is Gly (G) and the others are other than Gly (G).

20. (Amended) A multimeric ApoA-I agonist compound which [which exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural] comprises formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

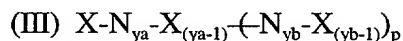
each "HH" is independently a peptide or peptide analogue according to

Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

21. (Amended) A multimeric ApoA-I agonist compound which [exhibits at least about 38% LCAT activation activity as compared with human ApoA-I and which has the structural] comprises formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently HH-(LL_m-HH)-_nLL_m-HH;

each HH is independently a [core] peptide [of structure (I) or an analogue or mutated, truncated, internally deleted or extended form thereof as described herein] or peptide analogue according to Claim 1;

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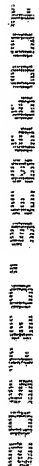
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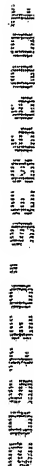
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or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $\text{HH}-(\text{LL}_m-\text{HH})_n\text{LL}_m-\text{HH}$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R₁ is -OR or -NRR; and

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, (C₅-C₂₀) aryl (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

23. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which the bifunctional linker is cleavable.

24. (Amended) The multimeric ApoA-I [multimeric] agonist compound of Claim 20, 21 or 22 in which n is 0.

25. (Amended) The multimeric ApoA-I agonist compound of Claim 24 in which m is 0.

26. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a peptide or peptide analogue according to Claim [13] 3.

27. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a peptide or peptide analogue according to Claim [14] 10.

29. (Amended) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist and a lipid, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

34. The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.

35. The ApoA-I agonist-lipid complex of Claim 34 which is in the form of a lyophilized powder.

37. (Amended) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

42. (Amended) The pharmaceutical composition of Claim 37[, 38, 39, 40 or 41] in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

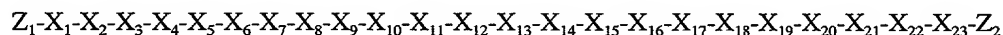
44. (Amended) A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist compound according to Claim 1.

54. (Amended) A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of the ApoA-I agonist compound according to Claim 1.

EXHIBIT B

Claim Amendment: Pending Claims After Entry of the Instant Amendment

1. (Amended) An ApoA-I agonist compound comprising:
- (i) a 22 to 29-residue D-enantiomeric peptide or peptide analogue which forms an amphipathic α -helix in the presence of lipids and which comprises formula (I):



or a pharmaceutically acceptable salt thereof, wherein:

X_1 is D-Ala (a), Gly (G), D-Gln (q), D-Asn (n), D-Asp (d) or D-Pro (p);

X_2 is a D-enantiomeric aliphatic residue;

X_3 is D-Leu (l) or D-Phe (f);

X_4 is a D-enantiomeric acidic residue;

X_5 is D-Leu (l) or D-Phe (f);

X_6 is D-Leu (l) or D-Phe (f);

X_7 is a D-enantiomeric hydrophilic residue;

X_8 is a D-enantiomeric acidic or a basic residue;

X_9 is D-Leu (l) or Gly (G);

X_{10} is D-Leu (l), D-Trp (w) or Gly (G);

X_{11} is a D-enantiomeric hydrophilic residue;

X_{12} is a D-enantiomeric hydrophilic residue;

X_{13} is Gly (G) or a D-enantiomeric aliphatic residue;

X_{14} is D-Leu (l), D-Trp (w), Gly (G) or D-Nal;

X_{15} is a D-enantiomeric hydrophilic residue;

X_{16} is a D-enantiomeric hydrophobic residue;

X_{17} is a D-enantiomeric hydrophobic residue;

X_{18} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

X_{19} is D-Gln (q), D-Asn (n) or a D-enantiomeric basic residue;

X_{20} is a D-enantiomeric basic residue;

X_{21} is a D-enantiomeric aliphatic residue;

X_{22} is a D-enantiomeric basic residue;

X₂₃ is absent or a D-enantiomeric basic residue;

Z₁ is R₂N- or RC(O)NR-;

Z₂ is -C(O)NRR, -C(O)OR or -C(O)OH or a salt thereof;

each R is independently -H, (C₁-C₆) alkyl, (C₁-C₆) alkenyl, (C₁-C₆) alkynyl, (C₅-C₂₀) aryl, (C₆-C₂₆) alkaryl, 5-20 membered heteroaryl, 6-26 membered alkheteroaryl or a 1 to 7-residue peptide or peptide analogue in which one or more bonds between residues 1 through 7 are independently a substituted amide, an isostere of an amide or an amide mimetic; and

each " - " between residues X₁ through X₂₃ independently designates an amide linkage, a substituted amide linkage, an isostere of an amide or an amide mimetic; or

(ii) a 14 to 28-residue deleted D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one and up to eight of residues X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, X₁₇, X₁₈, X₁₉, X₂₀, X₂₁ and X₂₂ are optionally deleted; or

(iii) a 22 to 29-residue altered D-enantiomeric peptide or peptide analogue according to formula (I) in which at least one of residues X₁, X₂, X₃, X₄, X₅, X₆, X₇, X₈, X₉, X₁₀, X₁₁, X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, X₁₇, X₁₈, X₁₉, X₂₀, X₂₁, X₂₂ or X₂₃ is conservatively substituted with another D-enantiomeric residue.

3. (Amended) The ApoA-I agonist compound of Claim 1 which is the altered D-enantiomeric peptide or peptide analogue according to formula (I).

4. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophobic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

5. (Amended) The ApoA-I agonist compound of Claim 4 in which:

X₁ is D-Pro (p), Gly (G) or D-Ala (a);

X₂ is D-Ala (a), D-Leu (l) or D-Val (v);

X₃ is D-Leu (l) or D-Phe (f);

X₅ is D-Leu (l) or D-Phe (f);

X₆ is D-Leu (l) or D-Phe (f);

X₉ is D-Leu (l) or Gly (G);

X₁₀ is D-Leu (l), D-Trp (w) or Gly (G);

X₁₃ is D-Leu (l), Gly (G) or D-Aib;

X₁₄ is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);

X₁₆ is D-Ala (a), D-Nal, D-Trp (w), Gly (G), D-Leu (l) or D-Phe (f);

X₁₇ is D-Leu (l), Gly (G) or D-Nal;

X₂₁ is D-Leu (l); and

at least one of X₄, X₇, X₈, X₁₁, X₁₂, X₁₅, X₁₈, X₁₉, X₂₀, X₂₂ and X₂₃ is conservatively substituted with another D-enantiomeric residue.

6. (Amended) The ApoA-I agonist compound of Claim 3 in which the D-enantiomeric hydrophilic residues are fixed according to formula (I) and at least one non-fixed residue is conservatively substituted with another D-enantiomeric residue.

7. (Amended) The ApoA-I agonist compound of Claim 6 in which:

X₄ is D-Asp (d) or D- Glu (e);

X₇ is D-Lys (k), D-Arg (r) or D-Orn;

X₈ is D-Asp (d) or D-Glu (e);

X₁₁ is D-Asn (n) or D-Gln (q);

X₁₂ is D-Glu (e) or D-Asp (d);

X₁₅ is D-Asp (d) or D-Glu (e);

X₁₈ is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X₁₉ is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;

X₂₀ is D-Lys (k) or D-Orn;

X₂₂ is D-Lys (k) or D-Orn;

X₂₃ is absent or D-Lys (k); and

at least one of X₁, X₂, X₃, X₅, X₆, X₉, X₁₀, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.

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8. (Amended) The ApoA-I agonist compound of Claim 7 in which X₃ is D-Leu (l) or D-Phe (f), X₆ is D-Phe (f), X₉ is D-Leu (l) or Gly (G), X₁₀ is D-Leu (l) or D-Trp (w) or Gly (G) and at least one of X₁, X₂, X₅, X₁₃, X₁₄, X₁₆, X₁₇ and X₂₁ is conservatively substituted with another D-enantiomeric residue.
9. (Amended) The ApoA-I agonist compound of Claim 4 or 6 in which the substituting D-enantiomeric residue is classified within the same sub-category as the substituted D-enantiomeric residue.
10. (Amended) The ApoA-I agonist compound of Claim 1 which is the deleted D-enantiomeric peptide or peptide analogue according to formula (I).
11. (Amended) The ApoA-I agonist compound of Claim 10 in which one or two helical turns of the peptide or peptide analogue is optionally deleted.
12. (Amended) The ApoA-I agonist compound of Claim 1 which is a 22-23 residue D-enantiomeric peptide or peptide analogue according to formula (I).
13. (Amended) The ApoA-I agonist compound of Claim 12 in which:
the "-" between residues designates -C(O)NH-;
Z₁ is H₂N-; and
Z₂ is -C(O)OH or a salt thereof.
14. (Amended) The ApoA-I agonist compound of Claim 13, in which:
X₁ is D-Ala (a), Gly (G), D-Asn (n), D-Gln (q), D-Asp (d) or D-Pro (p);
X₂ is D-Ala (a), D-Val (v) or D-Leu (l);
X₃ is D-Leu (l) or D-Phe (f);
X₄ is D-Asp (d) or D-Glu (e);
X₅ is D-Leu (l) or D-Phe (f);
X₆ is D-Leu (l) or D-Phe (f);
X₇ is D-Lys (k), D-Arg (r) or D-Orn;

X_8 is D-Asp (d) or D-Glu (e);
 X_9 is D-Leu (l) or Gly (G);
 X_{10} is D-Leu (l), D-Trp (w) or Gly (G);
 X_{11} is D-Asn (n) or D-Gln (q);
 X_{12} is D-Glu (e) or E-Asp (d);
 X_{13} is Gly (G), D-Leu (l) or D-Aib;
 X_{14} is D-Leu (l), D-Nal, D-Trp (w) or Gly (G);
 X_{15} is D-Asp (d) or D-Glu (e);
 X_{16} is D-Ala (a), D-Nal, D-Trp (w), D-Leu (l), D-Phe (f) or Gly (G);
 X_{17} is Gly (G), D-Leu (l) or D-Nal;
 X_{18} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
 X_{19} is D-Gln (q), D-Asn (n), D-Lys (k) or D-Orn;
 X_{20} is D-Lys (k) or D-Orn;
 X_{21} is D-Leu (l);
 X_{22} is D-Lys (k) or D-Orn; and
 X_{23} is absent or D-Lys (k).

15. (Amended) The ApoA-I agonist compound of Claim 14, in which X_{23} is absent.
16. (Amended) The ApoA-I agonist compound of Claim 13 or 14, in which one of X_{18} or X_{19} is D-Gln (q) or D-Asn (n) and the other of X_{18} or X_{19} is D-Lys (k) or D-Orn.
17. (Amended) The ApoA-I agonist compound of Claim 14 in which each of X_9 , X_{10} , X_{13} , X_{14} , X_{15} and X_{17} is other than Gly (G).
18. (Amended) The ApoA-I agonist compound of Claim 14 in which one of X_9 , X_{10} , X_{13} , X_{14} , X_{15} and X_{17} is Gly (G) and the others are other than Gly (G).
20. (Amended) A multimeric ApoA-I agonist compound which comprises formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

each m is independently an integer from 0 to 1;

n is an integer from 0 to 10;

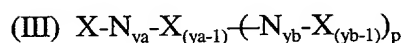
each "HH" is independently a peptide or peptide analogue according to

Claim 1;

each "LL" is independently a bifunctional linker; and

each " - " independently designates a covalent linkage.

21. (Amended) A multimeric ApoA-I agonist compound which comprises formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $HH-(LL_m-HH)_nLL_m-HH$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each m is independently an integer from 0 to 1;

each n is independently an integer from 0 to 8;

N_{y_a} and N_{y_b} are each independently a multifunctional linking moiety where y_a

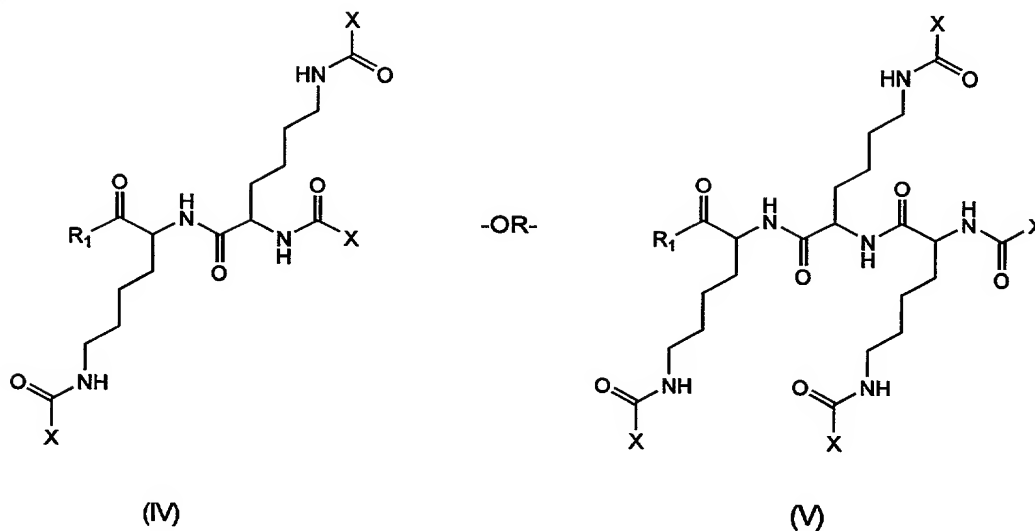
and y_b represent the number of functional groups on N_{y_a} and N_{y_b} , respectively;

each y_a or y_b is independently an integer from 3 to 8;

p is an integer from 0 to 7; and

each "—" independently designates a covalent bond.

22. (Amended) A multimeric ApoA-I agonist compound which comprises formula (IV) or (V):



or a pharmaceutically acceptable salt thereof, wherein:

each X is independently $\text{HH}-(\text{LL}_m-\text{HH})_n\text{LL}_m-\text{HH}$;

each HH is independently a peptide or peptide analogue according to Claim 1;

each LL is independently a bifunctional linker;

each n is independently an integer from 0 to 1;

each m is independently an integer from 0 to 8;

R_1 is -OR or -NRR; and

each R is independently -H, (C_1-C_6) alkyl, (C_1-C_6) alkenyl, (C_1-C_6) alkynyl; (C_5-C_{20}) aryl (C_6-C_{26}) alkaryl, 5-20 membered heteroaryl or 6-26 membered alkheteroaryl.

23. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which the bifunctional linker is cleavable.

24. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which n is 0.

25. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which m is 0.

26. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 21 in which each HH is independently a peptide or peptide analogue according to Claim 3.

27. (Amended) The multimeric ApoA-I agonist compound of Claim 20, 21 or 22 in which each HH is independently a peptide or peptide analogue according to Claim 10.

29. (Amended) An ApoA-I agonist-lipid complex comprising an ApoA-I agonist compound and a lipid, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

34. (Amended) The ApoA-I agonist-lipid complex of Claim 29 in which the lipid is sphingomyelin.

35. (Amended) The ApoA-I agonist-lipid complex of Claim 34 which is in the form of a lyophilized powder.

37. (Amended) A pharmaceutical composition comprising an ApoA-I agonist compound and a pharmaceutically acceptable carrier, excipient or diluent, wherein the ApoA-I agonist compound is a peptide or peptide analogue according to Claim 1, a multimeric ApoA-I agonist compound according to Claim 20, a multimeric ApoA-I agonist compound according to Claim 21, or a multimeric ApoA-I agonist compound according to Claim 22.

42. (Amended) The pharmaceutical composition of Claim 37, in which the ApoA-I agonist is in the form of an ApoA-I agonist-lipid complex, said complex comprising the ApoA-I agonist compound and a lipid.

44. (Amended) A method of treating a subject suffering from a disorder associated with dyslipidemia, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

54. (Amended) A method of treating a subject suffering from septic shock, said method comprising the step of administering to the subject an effective amount of an ApoA-I agonist compound according to Claim 1.

55. The method of Claim 44 or 54 in which said subject is a human.

56. The method of Claim 44 or 54 in which about 0.5 mg/kg to about 100 mg/kg ApoA-I agonist is administered to said subject.